I. REMARKS

Claims 4 and 37-44 are pending.

II. INTERVIEW

Examiner Woitach kindly agreed to an interview which was conducted on June 28, 2005. Present at this interview were David Perryman, David Huizenga, Robert Hodges, representing Applicant, James Kelly, Ph.D. of Amphioxus Inc. whose 37 C.F.R. § 1.132 Declaration accompanies this Response, and Examiner Woitach, Supervisor Deborah Reynolds, and Supervisor Ram Shukla. During this interview the remaining issues in the outstanding office action were discussed.

Applicants and Examiners discussed the legal standard for Written Description. It was agreed that actually making a claimed invention is one way of meeting the written description requirement, and thus making one of the claimed human cells could address the Written Description issue if the appropriate evidence was available (As the Patent and Trademark Office (PTO) had not seen the evidence discussed at the Interview, neither the Applicant nor the PTO, appropriately so, wanted a conclusion on the merits at the Interview) . In support of the statements, methods, and compositions in the present application, Dr. Kelly described the results of performing the methods presented in the present application and explained how the same human cells described in the application were obtained, and then how these cells have continued to behave and are characterized. Dr. Kelly's conclusion that the human cells set forth in the Experiments of the present application were in fact pluripotent stem cells as the art understood them at the time of the application and as the art understands this now was noted with interest by Examiner Woitach, and Supervisors Reynolds and Shukla.

The misconceptions and misunderstandings regarding the state of the art as to whether SSEA-1 positive cells were pluripotent was discussed. Statements made in the paper of "Comments Regarding Request for Interference" filed in Application No. 09/982,637 by WARF on October 19, 2004 regarding the nature of pluripotent stem cells, where it was indicated that the cells of the present application and the cells of Application No. 09/982,637 had absolutely no overlap, were discussed. No agreement on patentability of the present claims was requested, as the Applicant understands Examiner Woitach would need time to consider facts he was unaware

of before, but it was agreed that the evidence and argument discussed at the Interview was the type of information which could overcome the present rejections.

III. THOMSON/WARF FILE HISTORY STATEMENTS

Applicant notes that the statements made in the paper "Comments Regarding Request for Interference" filed in Application No. 09/982,637indicate that inventor/applicant Thomson and ownerWARF believe that their claims only cover SSEA-1 negative cells and do not include SSEA-1 positive cells. (Page 2, line 26 to page 3, line 13). Specifically, applicant/inventor Thomson and owner WARF state:

> "While there are many techniques that can be used to distinguish the cell types, for the purpose of this document, it is appropriate to refer specifically to the disclosures regarding these cells in the applicable patents. Primate (and human) ES cells are negative for a cell surface marker SSEA-1, and the attribute of being SSEA-1 is specifically claimed in Claim 3 of each of the '780 patent and the '806 patent and recited in this specification at page 8, line 12, page 22, line 11 to page 23, line 27.
>
> By contrast, the Gearhart patents report that human EG cells are dependent on the application of LIF. The LIF dependence is specifically recited in column 5, lines 42-55 of the Gearhart '662 patent. Human EG cells are also positive for the cell surface marker SSEA-1, as specifically recited in column 14, lines 6-10 and Claim 11 of the '662 patent.
>
> Thus from the technical description in the prior patent, there are established two classes of differences between EG cells and ES cells. One class of difference comes from the source or origin of the materials (inner cell mass of blastocysts for ES cells and primordial germ cells for EG cells) and other distinguishing difference in characteristic has to do with the biochemical differences in the cells themselves (LIF dependence and SSEA-1 presentation. ES cells and EG cells are distinct and separate cell types."

Applicant notes that if the PTO agrees with this position taken by WARF/Thomson, then the subject claims 39-44 would have no interfering overlap (by WARF/Thomson's admission) and thus the need for interference between applicants claims and WARF/Thomson claims would be moot.

IV. DOUBLE PATENTING REJECTION

Claims 4, 37-44 are presently provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 15, 18-21, and 23-28 of copending Application No. 10/327,400.

Applicants will provide a Terminal Disclaimer in compliance with 37 C.F.R. § 1.321(c) relative to Application No. 10/327,400. It is believed that this will obviate the present rejection pursuant to M.P.E.P. § 804.02.

V. REJECTION UNDER 35 U.S.C. § 112

Claims 4, and 37-44 are presently rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

First Applicant sees this rejection as coming down to a single issue. The PTO appears to believe that Applicant lacks adequate written description for human pluripotent stem cells, such as embryonic stem cells or embryonic germ cells, because the application, while being enabled for a method of making human pluripotent stem cells, allegedly does not provide a description of the cells themselves. The PTO appears to take this position because the limitations of claims 4, and 37-43 allegedly fail to distinguish the claimed cells from other cells and the limitations, both functional and structural limitations, do not "distinguish the cells from other cells" (Office Action at pages 4 and 5).

Before addressing the concerns of the PTO, Applicant emphasizes the points where the PTO and Applicant agree.

First, Applicant and PTO agree that the Applicant is enabled for making pluripotent stem cells in general. The Office Action states, "While the specification appears to provide a methodology to isolate stem cells in general, the specification fails to adequately describe the human cell that is isolated by that methodology." Page 5, lines 4-6. Applicants provision of a methodology to isolate stem cells in general was agreed to again at the Interview of June 28, 2005.

Second, Applicant and the PTO agree that reduction to practice in certain situations is sufficient for written description. The Office Action states, "*Possession may be shown by actual reduction to practice,* clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the invention as whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998)." Page 5,

lines 9-13. (emphasis added). The Office Action also states, "In the instant case, Applicants have asserted that the methods would result and have subsequently been used in the isolation a human stem cells, however it is maintained that the specification fails to describe the relevant identifying characteristics of such a human cell and *therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used."* Page 5, lines 13-18. (emphasis added). This point about the making of a claimed invention, such as a cell, is adequate written description for the cell was discussed at the Interview of June 28, 2005, and agreed upon.

A. Two differences remain between the Applicant and PTO

There remain two differences between the Applicant and the PTO regarding Applicant's present application. First, the legal requirements that markers be "essential elements" of a claim and second whether Applicant had made the cells claimed. Each of these is addressed in turn below. While Applicant believes that both of these issues are positive for Applicant's position, the rejection should be withdrawn if either of these issues are resolved in Applicant's favor.

1. Markers and "essential elements" of claims are sufficient

The PTO states in the Office Action, "It is noted that the specification teaches and the claims specifically set forth a series of histological markers the claimed human stem cell comprises, however, the specification fails to provide evidence that these markers are specific for human and post-filing art clearly teaches that certain makers are clearly not present on human stem cells." Page 4, line 21 to page 5, line 1. The Office Action goes on to state, "Further, beyond the differences in histological markers the ability to isolate and maintain a human stem cells has been demonstrated to be different from that used in isolating and maintaining mouse stem cells, for example in the ability of the isolated cell to respond to LIF in culture." Page 5, lines 1-4. Lastly, the Office Actions states, "The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of the Applicants effective filing date." Page 5, lines 6-9 , and "the specification fails to describe the relevant identifying characteristics of such a human cell" Page 5, lines 16-17. These statements are addressed below.

a) Applicant's response

(1) Some structure and function enough

As discussed at the Interview, Applicant maintains that as long as some structure has been provided and the function of the composition is provided, this is sufficient to meet the requirements of 35 U.S.C. § 112, first paragraph written description, as outlined by the Federal Circuit and in the PTO Guidelines on written description. The Federal Circuit stated in *Amgen Inc, v. Hoechst Marion Roussel, Inc, and Transkaryotic Therapies, Inc.*, 314 F.3d 1313; 1332 2003 U.S. App. LEXIS 118; 65 U.S.P.Q.2D (BNA) 1385, "More recently, in *Enzo Biochem*, we clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. See *Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613."* (For the Examiner's convenience the appropriate section of Enzo Biochem is provided in a footnote).[1]

(2) No requirement that the structure discussed be "essential" just "known"

Contrary to the position taken by the PTO, there is no requirement that the structure be essential, rather it is only required that the structure be known (note: that this can be interpreted

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[1] "It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement. The PTO has issued Guidelines governing its internal practice for addressing that issue. The Guidelines, like the Manual of Patent Examining Procedure ("MPEP"), are not binding on this court, but may be given judicial notice to the extent they do not conflict with the statute. See *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1180 n. 10, 33 USPQ2d 1823, 1828 n. 10 (Fed.Cir.1995). In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics*." Guidelines, 66 Fed.Reg. at 1106 (emphasis added). For example, the PTO would find compliance with 112, 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature. Synopsis of Application of Written Description Guidelines, at 60, available at http:// www.uspto.gov/web/patents/guides.htm (Application of Guidelines). Thus, under the Guidelines, ***the written description requirement would be met for all of the claims of the '659 patent if the functional characteristic of preferential binding to N. gonorrhoeae over N. meningitidis were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed.*** We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement." *Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613* (Italics, emphasis in original, and Italics-bold emphasis added)

to be "known" by the skilled artisan without disclosure in the application as both the Guidelines and the Federal Circuit state "known or disclosed" indicating that there can be a difference between known and that which is disclosed in the specification.). In *Amgen Inc. v. Hoechst*, the Federal Circuit stated, "TKT would have us view Gentry as a watershed case, in reliance on an isolated statement -- probably only dicta -- that one of ordinary skill in the art would clearly understand that the location of the reclining controls on the claimed sectional sofa "was not only important, but essential to [the] invention." *134 F.3d at 1480, 45 USPQ2d at 1503.* But as we recently indicated in *Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc., 291 F.3d 1317, 1323, 62 USPQ2d 1846, 1850-51 (Fed. Cir. 2002),* "we did not announce [in Gentry] a new 'essential element' test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements." See also *Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1114;* cf. *Aro Mfg. Co. v. Convertible Top Replacement Co., 365 U.S. 336, 345, 5 L. Ed. 2d 592, 81 S. Ct. 599, 1961 Dec. Comm'r Pat. 635 (1961)* ("There is no legally recognizable or protected 'essential element,' 'gist' or 'heart' of the invention in a combination patent."). *Amgen Inc, v. Hoechst Marion Roussel, Inc, and Transkaryotic Therapies, Inc.,* 314 F.3d 1313; 1333 2003 U.S. App. LEXIS 118; 65 U.S.P.Q.2D (BNA) 1385.

Thus, clearly when one takes *Amgen Inc. v. Hoechst* and the precedence it relies on (*Enzo Biochem*, for example) there is not an "essential element" test within the written description requirement (or within any other standard for the matter), and what is required is that some structure be known.

(3) Applicant's Have Provided Written Description

Under these standards, the limitations of Applicant's claims are clearly sufficient as one would understand whether one was in possession of the claimed pluripotent cells, i.e. understand the "known" structure and functions. Applicant's claims are directed to pluripotent human cells. Thus, as in *Amgen Inc v. Hoescht* (where the Federal Circuit held that vertebrate and mammalian cells were sufficiently described by a single species example within the genera), because the skilled artisan would know what they were, the "humanness" of the cells as presently claimed were and are known by those of skill in the art.

Applicants are providing known structure that further defines the cells in a way which the skilled artisan at the time would have understood the Applicant was in possession of the claimed

invention. For example, just like the antibody, as discussed in the PTO Guidelines and in *Enzo Biochem*, has a significant amount of defined structure, such as the FAB regions, a cell has many known structural elements, endoplasmic reticulum, nucleus, mitochondria, etc. Just like the function of the antibody binding antigen is sufficient to provide written description for the antibody, because of the "known" structure of the antibody, so to "known" structure of the claimed pluripotent human cell and the function of the pluripotency and differentiation into all cell types is sufficient to provide written description of a pluripotent stem cell. In combination with further structural characteristics, such as Alkaline phosphase positive (meaning the structure/presence of alkaline phosphatase in an active form) and the presence of SSEA-1, even more structure is provided.

Moreover, Applicant presently claims a "pluripotential stem cell" and an "embryonic pluripotential stem cell" which have defined structure, known structure, and defined function as one of skill in the art would understand if that cell was in the possession of the inventor at the time of the application. The defined structure includes normal karotype in claim 4 and further includes that the cell stains positive for the SSEA-1 antigen and stains positive for alkaline phosphatase in the dependent claims. The known structure includes what one skilled in the art would understand as the structure of a human cell (endoplasmic reticulum, mitochondria, and chromosomes, for example) as well as the structure one would understand that makes a cell pluripotent. The defined function is the cell's pluripotency, its ability to go through many passages, and its ability to differentiate into all three types of derm, mesoderm, ectoderm, and endoderm, as claimed. These characteristics, were what one would have used to define a pluripotent stem cell at the time of the invention and many years after applicants invention, are still how one would understand a pluripotent stem cell today.

Thus, irrespective of whether the Applicant reduced to practice the claimed human cells (which they did as discussed below), Applicant has met the Written Description standard in the way that they described the claimed human cells. Just as in *Amgen Inc. v. Hoechst,* a skilled artisan would understand the structure of a human cell (endoplasmic reticulum, mitochondria, and chromosomes, for example), the structure of a pluripotent call, additional structure provided in the specification and claims, and the function of the human "pluripotential stem" cell collectively demonstrate that applicant was in possession of the claimed cells.

b) Applicant had reduction to practice

Not that Applicant requires reduction to practice to have adequate written description, but in fact, Applicant did have reduction to practice of the claimed cells. In support of the contention that Applicant did in fact have the claimed cells, Dr. James Kelly has provided a 37 C.F.R. § 1.132 Declaration, which takes cells produced using the method used in the present application, and shows that these cells are the same cells as described in the application, as the skilled artisan would understand it. Dr. Kelly states, "Based on the following analysis of the '829 application it is my opinion that the application indicates to someone who understands cell culture and pluripotent stem cell culture and myself that Dr. Hogan had actually isolated human pluripotent stem cells, and she discussed these isolated cells in the application." (Page 2, lines 1-4)

The opinion of Dr. Kelly arose from his reading of the present application, and furthermore on experiments that confirmed that the method disclosed in the present application produces human pluripotent stem cells and these cells are the same as the cells described in the present application. Dr. Kelly states, "In addition to my opinion that the application makes clear that Dr. Hogan had isolated human pluripotent cells, experiments have been performed which confirm this opinion. While these experiments were not necessary for understanding that Dr. Hogan had isolated human pluripotent stem cells, these experiments prove that that the methods and cells discussed in the '829 application are human pluripotent stem cells." (Page 2, lines 4-8)

Dr. Kelly discusses the '829 application from pages 2 to 4 of his Declaration. Dr. Kelly finds that "from page 23, line 1 of the '829 application to page 24, line 4, the '829 application provides details about human pluripotent stem cells which were isolated. The methods used were like the methods used for the mouse, further indicating the universal applicability of the methods discussed in the '829 application."

Dr. Kelly focused on the following section of the '829 application which states, "The above methods for isolation of ES cells from murine embryos were repeated for isolation of ES cells from human embryos. Specifically, testes were dissected from a 10.5 week human embryo. Younger or older embryos represent alternative sources. The preferred age range is between 8.5 weeks and 22 weeks. Tissue was rinsed in buffered saline, and incubated in trypsin solution (0.25% trypsin, 1 mM EDTA in Ca^{30} + /Mg^{++} free HEPES buffered saline) for 10 minutes at 37

C. The tissue was dissociated by pipetting and the cells plated into wells of a 24 well tray containing irradiated feeder cells. In this experiment the feeder cells were Sl/Sl mouse fibroblasts transfected with human membrane associated Stem Cell Factor (Sl^4 h220 cells from Dr. David Williams, HHMI, Indiana State University School of Medicine). An alternative feeder layer would consist of a mixture of mouse or human embryo fibroblasts and Sl^4h220 cells, to provide a more coherent layer for long term cell attachment. The culture medium consists of Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum supplemented with 10 ng/ml human bFGF, 60 ng/ml human Stem Cell Factor and 10 ng/ml human LIF. Alternatively, the amounts of bFGF can be increased (e.g. 20 ng/ml). Other alternative or additional supplements can be added at this time, for example IL-6, IL-11, CNTF, NGF, IGFII, flt3/flk2 ligand, and/or members of the Bone Morphogenetic Protein family. The cultures were maintained for 5 days, with daily addition of fresh growth factors. Longer culture could also be utilized, e.g. 5 to 20 days."

The application further states, "After 5 days, cultures were dissociated with trypsin solution as before and seeded into wells containing a feeder layer of irradiated mouse embryo fibroblasts. The medium was supplemented with growth factors daily as above. The addition of growth factors to the culture medium at this stage can be utilized, and a feeder layer of a mixture of mouse of human fibroblast and Sl^4 h220 cells can be substituted." The application goes on to state, "After 10 days the cultures were fixed and stained for alkaline phosphatase activity. Colonies of cells expressing high levels of alkaline phosphatase and closely resembling primordial germ cells of the mouse embryo were detected in many wells (see FIG. 5). Closely packed clusters of cells were present in some colonies (arrow in FIG. 5). In cultures of mouse embryo germ cells these colonies give rise to lines of pluripotential embryonic stem cells. Therefore, the identified human cells can give rise to cell lines."

Dr. Kelly concludes from these sections in the '829 application that "It is clear from this section of the '829 application that the alkaline phosphatase positive cells were pluripotent stem cells as discussed throughout the '829 application. This is clear because not only did the cells express the alkaline phosphatase, but the cells also resembled the mouse primordial germ cells and the alkaline phosphatase positive cells were in clusters, both characteristics present in the mouse pluripotent stem cells as discussed through out the '829 application. At this point the

human pluripotent stem cells had been isolated and were growing and identifiable in the culture." Thus, the cells identified in the above-identified sections of the '829 application were indeed human pluripotent stem cells.

In addition to commenting on the '829 application, Dr. Kelly also refers to a series of experiments to show that that the methods in the '829 application do work as indicated, which will give the Examiner an understanding that in fact these cells were described by the Applicant as the cells produced from the method are the cells described in the application.

Dr. Kelly states, "These experiments, described below, replicated the methods described in the '829 application. The results paralleled those described in the '829 application. Furthermore, when the cells described in the application as the human pluripotent stem cells were further cultured they behaved with all of the characteristics described in the '829 application such as the ability to be passaged at least 20 times and the ability to form embryoid bodies having cells from mesoderm, endoderm, and ectoderm present.

The following results are described:

a. A nine week old, male fetus was obtained by Dr. Rob Hay at the American Type Culture Collection. Gonadal ridges were dissected and tissue was dissociated with 0.25% trypsin, 0.03% EDTA. Dissociated cells were plated into two 12.5 cm^2 flasks containing irradiated STO cells as a feeder layer. Cultures were fed with DMEM containing 15% fetal bovine serum (FBS), 1mM glutamine, 0.1 mM nonessential amino acids, 0.1mM beta-mercaptoethanol, 60 ng/ml human stem cell factor, 10 ng/ml human basic fibroblast growth factor, 10 ng/ml human leukemia inhibitory factor, 100 U/ml penicillin, 100 µg/ml streptomycin. Medium was replaced daily.

b. On day 5, one flask was stained for alkaline phosphatase. There were many positive cells.

c. Cells were passaged on day 6 using 0.05% trypsin, 0.015% EDTA and diluted into four 12.5 cm^2 flasks containing irradiated STO feeder layers. Medium was replaced daily.

d. On day 11, one flask was stained for alkaline phosphatase, showing many positive cells. Cells were trypsinized as above, pooled and plated into two 75 cm^2 flasks and two 12.5 cm^2 flasks containing irradiated STO feeder layers. Medium was replaced daily.

e. On day 20, the cells from the two 75 cm^2 flasks and one 12.5 cm^2 flask were collected by trypsinization, suspended in DMEM containing 15% fetal bovine serum and 10% dimethylsulfoxide and distributed into five 1.5 ml, screw cap freezer vials. Vials were frozen in a controlled rate freezer to a temperature of –80°C, then moved into a liquid nitrogen freezer.

f. Several vials of frozen cells were shipped from Dr. Hay to Dr. Kelly. A single vial of cells was thawed by Dr. Kelly and diluted into 10 ml of the DMEM medium described above without the antibiotics. Cells were plated into two wells of a 6 well dish containing mitomycin C treated STO cells. Medium was replaced three times per week. Growth of cells on top of the feeder layer was evident within two days. The cells grew as rounded clusters, evident by their morphology, on top of the flat, fibroblast feeder cells. By day 7, the medium needed to be changed daily due to pH changes. On day 10, one well was stained for alkaline phosphatase. A nearly confluent monolayer of alkaline phosphatase positive cells was apparent. The other well was trypsinized as described above and the cells were diluted into 15 mls of fresh medium. These were plated into a 75 cm^2 flask containing mitomycin c treated STO cells. Thereafter, cells were trypsinized at approximately ten day intervals and diluted one to five into new flasks containing mitomycin c treated STO cells. This continued for approximately 150 days or an additional 15 passages. At 2.5 doublings per passage, this is a 2^{40} or over a 1 trillion fold expansion of the cells from the frozen vial. Essentially 100% of the cells remain alkaline phosphatase positive.

g. Human EG cells were cultured as described above on chambered microscope slides. On day five, cells were washed once with phosphate buffered saline and fixed by treatment with 100% methanol at 4°C for five minutes. Monoclonal antibodies against stage specific embryonic antigen 1 (SSEA1), TRA 1-60 and TRA 1-80 were obtained from Santa Cruz Biotechnology. Antibodies were incubated with the cells at a one to fifty dilution in phosphate buffered saline for two hours at room temperature. Cells were washed three times with PBS then incubated with appropriate second antibodies, either anti mouse IgG or anti mouse IgM. Reaction was detected by staining with an avidin biotin based kit also obtained from Santa Cruz. Cells were positive for all three antigens. Preimmune mouse IgG and IgM were used as controls and showed no reaction.

h. Two 75 cm^2 flasks of human EG cells at approximate passage 21 (the end of the expansion described above) were shipped to Applied Genetics Laboratory in Melbourne, FL, for karyotyping. They found that the cells in the culture, based on 100 metaphases examined, had a modal chromosome number of 46 and 91% of the cells had between 44 and 46 chromosomes. No chromosome aberrations, defined as deletions, inversions or interchanges of genetic materials, were found in the 100 metaphase cells examined. Thus, the karyotype was normal.

j. Human pluripotent cells were trypsinized as described above and resuspended in Med3, which is a mixture of Ham's F12, Williams E and Waymouth's MAB containing 5% defined calf serum. The cell suspension was placed into a non adherent plastic container and incubated without medium change for five days. Within twenty four hours, most of the cells had formed aggregates of cells. In an additional 24 hours, most of the aggregates had formed hollow-centered balls of cells, so called embryoid bodies. At five days, half of the medium was removed and replaced. Aggregates began to show signs of developing an external layer

> of differentiated cells with a different morphology than the internal cells. Aggregates expanded considerably in size. An aliquot of the medium containing the embryoid bodies was removed and cells were collected by centrifugation. Cells were suspended in fresh Med3 and plated in the wells of a 6 well tissue culture dish. Most aggregates adhered to the surface of the wells and cell proliferation was evident. Within ten days, most wells contained nearly confluent layers of cells with a significantly different morphology than the untreated pluripotent stem cells.

Dr. Kelly concludes from these experiments that the method described in the '829 application does in fact produce the cells described in the '829 application. Dr. Kelly states, "Thus, the '829 application not only taught how to make human pluripotent stem cells, the '829 application also discusses a completed isolation of human pluripotent stem cells. The cells were in the hands of the Inventor, listed as Dr. Brigid Hogan, based on what is disclosed in the '829 application."

B. Conclusion

In conclusion, claims 4, and 37-44 have adequate written description on two grounds. First, the law requires that a "known or disclosed" structure be provided with a function of the claimed composition, such that a skilled artisan would understand that the inventor was in possession of that claimed. Just as in *Amgen Inc. v. Hoechst*, the subject application discloses a cell, a human cell, which in *Amgen* was found to have all sorts of known structure, common to human cells, such as the endoplasmic reticulum or the nucleus. A skilled artisan knows then and now when they are looking at a human cell. This leaves the issue of "pluripotential stem" then as the claims are drawn to pluripotential stem cells and "pluripotential embryonic stem" (as defined in the subject application). *Amgen* and *Enzo* then require us to look for a structure/function to go with the known structure of the pluripotent human cell, which was, as it is today, described by the passage capabilities of the cell and by the differentiation capabilities of the cell, just as provided in the claim. On this line of thinking, lastly, the point addressed by the Examiner, that the structure of the essential element must be known or present was shown to be

overreaching by the discussion of *Amgen Inc. v. Hoechst*, above. The added structural limitations of being alkaline phosphatase positive and SSEA 1 positive add further structural limitations to the claimed subject matter.

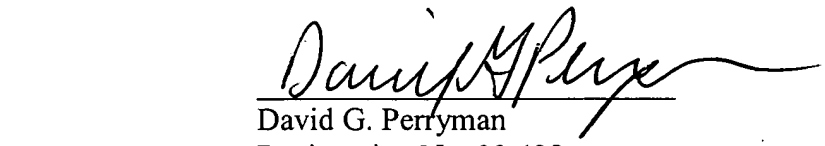
In addition, evidence was submitted in the form of a Declaration that 1) the cells described in the '829 application were in fact produced in the '829 application, and 2) the methods in the '829 application were performed and showed that they produced cells as described in the '829 application and with the characteristics as claimed. Thus, under a separate standard set forth in Enzo, actually possessing the cells, Applicants have shown that they had the cells at the time the '829 application was filed.

These two reasons either individually or together should moot the present written description rejection. Reconsideration of the claims is respectfully requested. Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $510.00, representing $510.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(3), a Declaration by James Kelly, Ph.D. under 37 C.F.R. § 1.132, and a Request For A Three-Month Extension Of Time, are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



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